

Attorney Docket No.: **WSTR-0014C**
Inventors: **Shiekhattar, Ramin**
Serial No.: **10/634,574**
Filing Date: **AUGUST 5, 2003**
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Amendments to the Specification:

Please replace the paragraph beginning on line 22 of page 15 with the following rewritten paragraph:

--It has now been shown that BRCA1 and BRCA2 are part of a multiprotein complex termed BRCC. A number of novel components of BRCC have been described including BRCC36 (~~SEQ ID NO:9~~ SEQ ID NO:10), a protein with sequence homology to a subunit of the signalosome and proteasome complexes, and BRCC45/BRE (~~SEQ ID NO:8~~ SEQ ID NO:9), a protein that is enriched in the brain and the reproductive organs. Further associated with BRCC is BRCC140 which shares homology with ubiquitin hydrolases. Detailed analysis of these new components of the complex revealed that, similar to BRCA1, depletion of BRCC36 and BRCC45/BRE resulted in increased sensitivity to ionizing radiation and loss of G2/M checkpoint arrest. Further, BRCC36 inhibits the ubiquitin E3 ligase activity and transcriptional regulator activity of BRCC and BRCC140 may function to deubiquitinate BRCC substrates. Moreover, cancer-causing truncations of BRCA1 destabilize the complex and abrogate the association of BRCC36 and BRCC45/BRE with BRCC. These findings identify BRCC, a complex containing hereditary breast cancer susceptibility genes mediating cellular responsiveness to DNA damage. Accordingly, one aspect of the present invention relates to a method of regulating the activity of at least one component of BRCC via an agent which alters the expression or activity of a BRCC36 or BRE subunit of BRCC. The method involves contacting BRCC or a cell containing BRCC with an agent that interacts with a nucleic acid sequence encoding BRCC36 or BRE, or a product thereof, so that the level of expression or

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activity of BRCC36 or BRE is altered thereby modulating an activity of at least one component of a BRCC. As used herein, a product of a nucleic acid sequence encoding BRCC36 or BRE is intended to include the BRCC36 or BRE mRNA transcript and BRCC36 or BRE protein.--